

# Pharmaceutical counseling about the application of non-conventional dosage forms

Ph.D. thesis

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## INTRODUCTION

According to the effect of the well-chosen dosage forms or the complexity of the therapy, the special and unified pharmaceutical counseling is needed about the different dosage forms especially about the application of non-conventional formulations. Although patients' adherence related to the application of non-conventional dosages forms is relatively high compare to the other dosage forms, the lack of the correct application could decrease the effectiveness of the therapy. In the community pharmacies, the reliable professional knowledge of pharmacists is essential to the effective advising and the patients have to learn the new application rules about the innovative dosage forms to the maximally effective and safe therapies in their home.

The Medication Regimen Complexity Index (MRCI) can present the complication of a therapy concerning all medicines of a patient. This index number includes the pharmaceutical dosage forms of medicines, the difficulties of dosing frequency and additional dosage or applications instructions among others. If this number is high, the risk of low adherence is also high during the therapy on the basis of surveys.

In the time of non-infectious diseases, more and more patients have to take many different medicines parallel. The polypharmacy will be more effective if the medicines' application is correct. The applications errors should be known and prevented. Many international researches have contributed to more effective and safer therapies because the more medicines mean higher risk of safety.

The most important application rules of the modified release controlled tablets and capsules are the questions with the tablet-halving (tablet-splitting), the tablet-crushing (tablet-chewing) or the capsule-opening (content-crushing/chewing) during the pharmaceutical advising. These problems can become serious if the patients arbitrarily split or crush their tablets (capsules) without the adequate knowledge of dosage forms (e.g., if they cannot swallow these oral dosage forms in whole for any reason).

Although the transdermal medicinal patches have several advantages, the patients have to know the application rules for the most effective and safe therapy. This application rules are general information about the correct use of this dosage form regardless of the Active Pharmaceutical Ingredient (API) or pharmaceutical, technological formulation of patches. The pharmacists should draw the patients' attention to these application rules in community pharmacies because the responses of the practical problems are not often in

the manufacturers' Patient Information Leaflet (PIL). Serious or lethal medication errors can be avoided with the advising of these practical application rules (e.g., using fentanyl as API).

The most of patients have questions concerning their self-care on the basis of surveys or practical experience and the healthcare professionals should answer these. Although different professionals take care for the patients to the safe and effective home-therapy, the knowledge of the pharmaceutical dosage forms is a pharmaceutical competence or pharmaceutical role in the healthcare. The special knowledge of pharmacology, pharmaceutical technology or pharmaceutical care contributes to the pharmaceutical advising about the several non-conventional formulations.

The pharmacists should explore the patients' medication application habits or their application errors. The level of patients' health literacy should be measured and improved e.g., reading comprehension. On the basis of reading comprehension tests in the community pharmacy, useful and understandable PILs can be developed for the patients. Similar studies can contribute to the reduction of the information asymmetry in the healthcare. The pharmaceutical counseling can improve the level of health literacy and adherence of patients and it also increases the cost-effectiveness and therapeutic effectiveness.

## **AIMS OF THE STUDIES**

- The patients' application habits or their application errors were explored concerning the modified release controlled tablets/capsules and the transdermal medicinal patches. The questionnaire surveys can contribute to the improving of the pharmaceutical counseling about the application of examined non-conventional dosage forms in the practice [1, 2].
- Written PILs were developed with evidence based information and our own results later. Concerning the two examined dosage forms' application, our PILs can improve the health literacy of patients with practical and understandable information [1, 2].
- In case of the transdermal medicinal patches, the usefulness and expedience of our self-developed written PIL were measured with a reading comprehension questionnaire survey in Hungarian community pharmacies [3].
- Professional guide-lines were developed for the pharmacists concerning the advising of the two examined dosage forms on the basis of evidence based information because the further training of pharmacists is needed for the patient oriented services [1].
- Concerning the halving of the splittable tablets, the different splitting methods were examined if the halving is not avoided during the therapy (correct dosing). During the investigations, a self-developed splitting device was tested with mechanical modeling. On the basis of the results, a decision-making scheme for the selection of tablet-splitting methods was developed. This scheme can improve the safety and effectiveness of therapies if the halving is unavoidable [4].
- The public opinion about demand of verbal pharmaceutical counseling related to the application of other non-conventional dosage forms was explored with our questionnaire surveys in community pharmacies. It can contribute to definition of required services of the pharmaceutical care in Hungary [3].
- Intervention options can be located in community pharmaceutical practice as part of the indispensable drug safety control performed in the basic level of the pharmaceutical care in Hungary [1, 2, 3, 4].

## METHODS

The questionnaire survey related to application habits of modified release controlled tablets/capsules was determined in two Hungarian community pharmacies with self-developed questions (from October of 2012 to November of 2012). Each patient was voluntarily participated in the survey. Man and women over 18 years of age answered the question on paper in order to achieve the overall target population (elder age group). The test paper included five, closed-type questions (as statements) with scaled answers (short concise structure and not in suggestive question-type). The five-point scale was a frequency scale of habits. Each patient was taking at least one not splittable (not crushable or not chewable) tablet or capsule beside their conventional release oral dosage forms. According to the selection of patients, it could be assumed that the patients knew the difference between the application rules of conventional and modified release controlled oral, solid dosage forms if they cannot swallow these in whole for any reason [1].

The questionnaire survey of application habits of transdermal medicinal patches was administered in thirteen Hungarian community pharmacies with self-developed questions (from October of 2012 to May of 2015). The participants were over 18 years of age (man and woman) who were using some transdermal medicinal patches. Each patient was voluntarily participated in the survey. The test paper included six closed-type questions and the participants could answer with a five-point scale (frequency scale) [2].

In the cases of both questionnaire surveys, the participants answered in the pharmacies without counseling and helping. After the surveys, the patients received a self-developed PIL about the general application rules of the used non-conventional dosage form. After data collecting, descriptive statistic and comparative tests were performed ( $\chi^2$ -test). During processing of responses, the five-point scale was transformed into a two-point scale. The “clearly correct” answer was separated from the other four in the following “wrong” answers [1, 2].

The useful (understandable for patients) of a further developed PIL related to the general application rules of transdermal medicinal patches was measured with a reading comprehension questionnaire survey in four Hungarian community pharmacies (from March of 2016 to April of 2016). Each patient voluntarily participated in the survey. Men and women over 18 years of age answered the questions on paper in pharmacies and the “patch ever adopters” or “patch never adopters” have answered for our questions. The

test paper basically organized from three parts, as follows: questions regarding demography and personal use of transdermal medicinal patches; the developed text of PIL concerning the most important application rules of transdermal medicinal patches; reading comprehension tasks and a question concerning the additional request of the patients. In the course of the answering of the part of reading comprehension test it was allowed to use the PIL without personal assistance of the staff. The reading comprehension test consisted of five true/false type tasks and a multiple-choice task. The last question explored to public opinion about demand of verbal counseling related to correct use of further non-conventional drug formulations. Four reading comprehension levels have separated with an eight-point scale based on the maximum available eight points. The four categories are as follows: “inadequate” (0 – 2 points); “low sufficient” (3 – 4 points); “high sufficient” (5 – 6 points); “adequate” (7 – 8 points) level of reading comprehension. The descriptive statistic and the comparative tests were performed ( $\chi^2$ -test and Kruskal-Wallis-test for age groups analyses) [3].

For the selection of appropriate splitting-methods, weighing test was basically measured during the examinations. Four types of splittable, conventional release tablets were halved with four splitting methods (Algozone<sup>®</sup>, Algopyrin<sup>®</sup>, Metapyrin<sup>®</sup> and Bisoprolol Sandoz<sup>®</sup>). Each tablet has a marketing authorisation license in Hungary. Four external properties were selected according to the appearance of the tablets, as follows: round/caplet, film-coated/non-film coated, half (quarter)-scored/unscored and small/large tablets [4].

For all four types of tablet, about fifty tablets were halved with four splitting methods, using a unified measurement plan. The measurement was done by each tablet type as follows: about 50 tablets were broken by hand (all tablets were broken by the same person: female, 27 years old, healthy); about 50 tablets were split with a kitchen knife; about 50 tablets were split with a type 1 tablet-splitting device; about 50 tablets were split with a type 2 tablet-splitting device (developed according to self-mechanical modelling) [4].

Weighing tests were measured with an analytical balance in the laboratory of a community pharmacy (from December 2016 to February 2017). Further physical and mechanical parameters were measured with hardness and friability tests. These parameters contributed to the more detailed evaluation [4].

After the mechanical modeling of the selected tablet splitter (manufacturer: Wolf<sup>®</sup>), the primary aim of the mechanical development was to reduce displacement or sliding of tablets in the splitter when closing the blade, to decrease the weight loss of the modified device for hard and large tablets (e.g., film-coated tablets). This is a high priority problem to solve; breaking these film-coated tablets can be difficult by hand, and dangerous with a kitchen knife, because of the coating and the tablet's hard inner core (Metapyrin<sup>®</sup>). Also, the geometry of tablets was analysed according to shape of examined tables (round-shaped tablets, caplet-shaped tablets of sharp or rounded edges) [4].

The differences and correlations were analysed among the four types of tablets and the four types of splitting methods. The weight loss and precision of the splitting methods were determined to compare the tablet-splitting methods and the two types of tablet splitter. Even, the frequency of over tablet-breaking was investigated according to methods and tablet's types. The definition of weight loss as follow: weight variation between the weight of the whole tablet and the weight of two half-tablets. The precision means that, weight variation between the weight of the right half-tablet and the weight of the left half-tablet. Over tablet-breaking is defined as a tablet broken into more than two parts (e.g., three or more smaller divisions) during the splitting. These events were separated from the weight loss analysis because these cases were not interpretable regarding tablet-halving [4].

The difference between splitting methods (by hand, with knife, with type 1 and type 2 splitting devices) was determined with variance analysis for each type of tablet (Algopyrin<sup>®</sup>, Algozone<sup>®</sup>, Metapyrin<sup>®</sup> and Bisoprolol Sandoz<sup>®</sup>) [4].

The four tablet-splitting methods and the two types of tablet splitter were compared with variance analysis concerning the three, larger tablets' measurements (Algopyrin<sup>®</sup>, Algozone<sup>®</sup>, Metapyrin<sup>®</sup>) [4].

Paired comparison was also performed with the Bonferroni-test to compare the four splitting methods and the two types of tablet splitter for weight loss and precision. In addition, we used a  $\chi^2$ -test to investigate the frequency of over tablet-breaking [4].

## NEW RESULTS

### **The most important results of the questionnaire survey related to the application habits of modified release controlled tablets/capsules [1]**

- The participated patients (n=75 persons) split their tablets most often if they cannot swallow these for any reason (57 percent from 57 patients). It means that the tablet-splitting comes to the patients' mind more often than the tablet-crushing (35 percent from 57 patients) or capsule-opening if they have swallowing problem. The difference is significant between the frequency of tablet-splitting and tablet-crushing ( $\chi^2=7.756$  és  $p=0.005$ ). On the basis of this result, the tablet-splitting is a relevant and arbitrary problem from the three assumed behaviors among patients.
- According to the low frequency of the "clearly correct" answers in the cases of the first three questions, the difference is not known by patients between the conventional and modified release controlled oral, solid dosage forms according to the application rules of the tablet-splitting ("clearly correct" answers: 13 percent), the tablet-crushing ("clearly correct" answers: 7 percent) and capsule-opening ("clearly correct" answers: 9 percent). Although the manufacturers' PILs include similar information and each participated patient was taking least one not splittable (crushable) oral, modified release controlled dosage form beside their conventional tablets/capsules. This part of the patients' health literacy is rather deficient.
- According to the previous two results, more than half of the participated patients split the tablets with some frequency but only a few patients know which tablets can be splitted. The splitting of the modified release controlled tablets means a relevant safety and effectiveness hazard in practice.
- On the basis of the results, less than half of the participated patients crush the tablets or open the capsules if they cannot swallow these in whole. 35 percent of participants crush the tablets with some frequency and 20 percent of participants open the capsules with some frequency for their own consideration. The difference between the frequency of the tablet-splitting and tablet-crushing is significant ( $\chi^2=7.756$  and  $p=0.005$ ) and the frequency of the capsules-opening is significantly less than the frequency of tablet-splitting or tablet-crushing ( $\chi^2=25.399$  and  $p=0.00004$ ). It can



cause non-adherence during the therapy according to conventional and splittable or crushable tablets and capsules.

**The most important results of the questionnaire survey related to the application habits of the transdermal medicinal patches [2]**

- On the basis of this survey's results, the pharmaceutical counseling about the general application rules of the transdermal medicinal patches is obviously required in the community pharmacies because only a few patients (9 persons) could response to the questions without "wrong" answer from the all participants (n=233 patients). It means that the effectiveness and the safety of therapies with patches can decrease in the cases of the most of participated patients (224 persons). The general application rules and the functioning of the transdermal medicinal patches are not known by the patients who are using this dosage form.
- According to this questionnaire survey, the pharmacists should inform patients about the most frequent application errors related to the transdermal medicinal patches. They should alert them to avoid the use of soap for skin cleansing before a patch is affixed (the most common error, the frequency of "wrong" answer is 78.11 percent) and that every patch must be affixed to a different location on their body, if possible (the second common error, the frequency of "wrong" answer is 70.0 percent). The difference is significant between the frequency of all application errors ( $\chi^2=192.075$  és  $p<0.001$ ).

**The most important results of the reading comprehension questionnaire survey related to the self-developed written PIL about the general application rules of transdermal medicinal patches [3]**

- On the basis of the compared tests of this survey (n=163 persons), the difference is not significant ( $p=0.428$  with 95 percent confidence intervals) between reading comprehension of "patch ever adopters" (92 persons) and "patch never adopters" (71 persons). The latter demonstrates that the patients were not familiar with these practical application rules of transdermal patches who have been used this dosage form. In community pharmacies, the pharmacists should inform patients about the

importance of correct home medicine use and the counseling is obviously required in the practice.

- The self-developed PIL has been understandable for the patients concerning the correct use of transdermal medicinal patches because in most of cases (86 percent) the level of reading comprehension was “adequate” (46 percent) or “high sufficient” (40 percent) based on the results of reading comprehension tasks (the “low sufficient” level of reading comprehension is 12 percent and the “inadequate” level of reading comprehension is 2 percent).
- Although the written instructions have proved useful, 54 percent of participants has lack of proper understanding (“high / low sufficient or inadequate” level of reading comprehension). The PIL should not replace the verbal counseling and patient education related to this dosage form. The pharmacist should pay a special attention to patients over 50 years of age in order to reach an effective and safe home use of transdermal patches (the result of Kruskal-Wallis test is nearly significant,  $p=0.051$ ). The multiple choices were the most difficult task in reading comprehension test opposite the true/false type questions ( $p<0.001$  és  $\chi^2=87.519$  and only 37 percent of responses were correct). The self-developed PIL is useful to give the transdermal patch adopters in community pharmacies along with the point by point verbal explanations.
- The responses of the special request concerning the pharmacists’ information service show the demand of personal pharmaceutical counseling related to non-conventional dosage forms in community pharmacies. 80 percent would require this service. There is a definite demand for verbal counseling concerning the application rules of (further) non-conventional dosage forms.

#### **Comprehensive evaluation of investigations related to the development of the decision-making shame of splitting methods in cases of the splittable tablets [4]**

- The questions concerning the tablet-splitting of splittable tablets are complex and not simply answered.

- The external features (size, geometry, film-coat and score-line) and mechanical parameters (hardness and friability) of tablets and the mechanical structure of splitting devices can influence the weight loss and precision of tablet splitting on the basis of the results of variance analyses and according to the frequency of over tablet-breaking ( $\chi^2$ -test).
- In addition, the skill of the patient and the characteristics of the therapy should be known for reliable counselling.

## CONCLUSIONS

### **Intervention opportunities in the community pharmacies in Hungary:**

- The splitting information of the modified release controlled tablets should emphasize as a part of verbal counseling according to the safe and effective application of this dosage form at least for the first time in the community pharmacies, because the tablet-splitting can become necessary if the patients cannot swallow the tablets in whole. The first counseling will be done by a pharmacist [1].
- It is needed that the health literacy of patients related to the modified release controlled tablets/capsules will be improved in the community pharmacies. Our self-developed written PILs including “ask your pharmacist for more information” and the verbal counseling can contribute to the pharmaceutical care. In addition, our evidence based and self-developed guideline can be useful in practice [1].
- Outer packaging of all not crushable and/or not splittable modified release controlled tablets/capsules should be signed with simple alerts messages. The splitting and/or crushing would be allowed without these messages [1]. For example:

**Not crush or split the tablets in any way!**

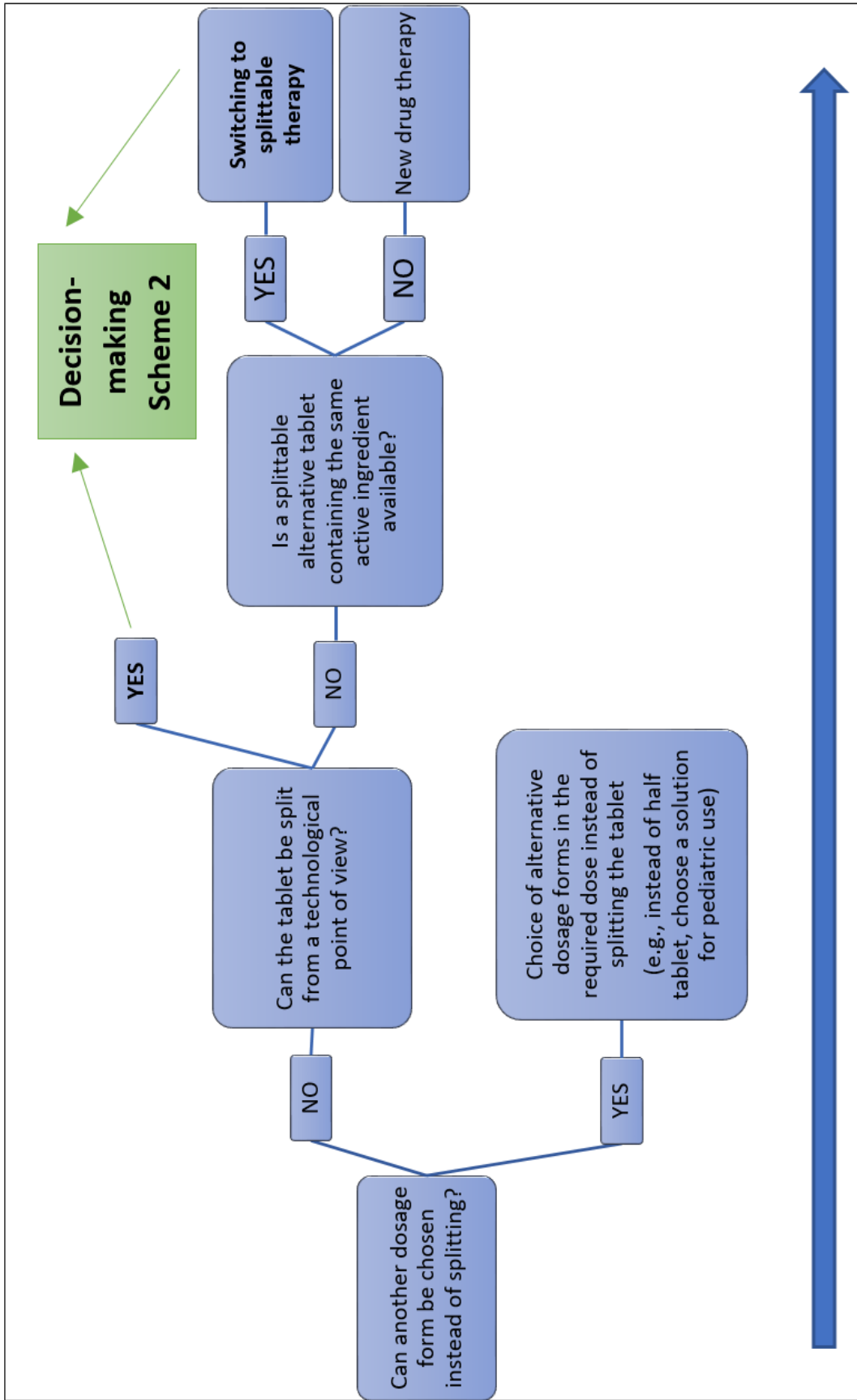
**Not crush the tablets in any way but the splitting is allowed!**

**Swallow the capsules in whole!**

**If it is necessary to open the capsule, not crush or chew the content in any way!**

- The verbal counseling about the application rules of transdermal medicinal patches is necessary with the patients at least in the first time in community pharmacies. The first counseling will be done by a pharmacist. Our self-developed written PIL can improve this advising and the information of manufacturer’s PIL is important also [2].

- During the verbal counseling about the transdermal medicinal patches, the pharmacists should inform patients about the most frequent application errors alerting them to avoid the use of soap for skin cleansing before a patch is affixed and that every patch must be affixed to a different location on their body [2].
- The verbal pharmaceutical advising related to the application of transdermal medicinal patches should be always offered for the patients in the community pharmacies. Our self-developed written PIL is proved useful concerning this dosage form and it can be easily and uniformly introduced in all community pharmacies in Hungary [3].
- If it is possible, the written PILs should be given after the verbal, pharmaceutical counseling at least in the first time [3].
- Similar to the showed surveys, other relevant application problems can explore related to further (non-conventional) dosage forms in community pharmacies [1, 2, 3].
- Although a written PIL (or the online advising) can be useful, the verbal communication is an important part of the quality and targeted counseling in the future also [3].
- Pharmacists should pay attention to many factors when counselling patients about the tablet-splitting for the precise dosing. Some general aspects and questions can be useful and contribute to the development of helpful pharmaceutical counselling in the community pharmacies. *Figure 1* and *Figure 2* show our self-developed decision-making outline for the selection of tablet-splitting methods in two steps [4].



**Figure 1:** Decision-making Scheme 1 (safety and effectiveness) [4]

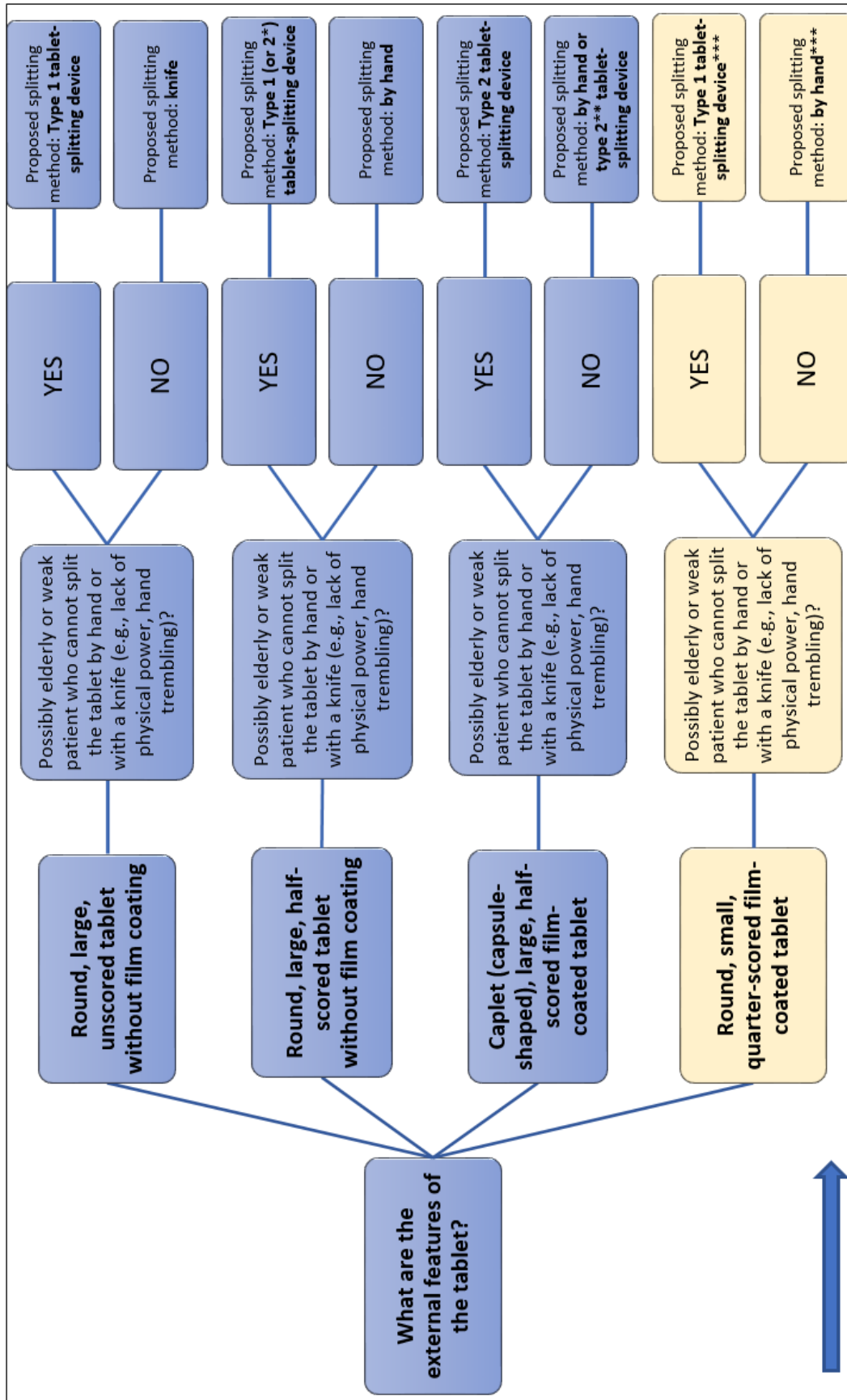


Figure 2: Decision-making Scheme 2 (more effectiveness) [4]

\*For Algopyrin<sup>®</sup>, the difference was not significant between the two types of splitting devices. If it is required, the type 2 splitting device can be proposed.

\*\*For Metapyrin<sup>®</sup>, the type 2 splitting device was significantly better for accuracy, but breaking by hand was significantly better for precision. Similar tablets are too hard to be broken by hand; hence, the type 2 splitting device should be proposed.

\*\*\*For Bisoprolol Sandoz<sup>®</sup>, the difference was significant between the splitting methods on the basis of the over tablet-breaking analysis.



## LIST OF ORIGINAL PUBLICATIONS

### Publications connected to the Ph.D. thesis

1. **Somogyi O**, Zelkó R. (2016) Nem konvencionális gyógyszerformákkal kapcsolatos gyógyszerészi tanácsadás az egészségműveltség és a beteg-együttműködés tükrében a közvetlen lakossági gyógyszerellátás során - Kérdőíves felmérések hazai közforgalmú gyógyszertárakban. *Acta Pharm Hung*, 86: 113-127.
2. **Somogyi O**, Zelkó R. (2016) Patient's knowledge of medical patches in Hungary. *Acta Pol Pharm*, 73: 1653-1657.
3. **Somogyi O**, Zelkó R. (2017) The efficacy of written information about the application rules of transdermal patches – reading comprehension questionnaire survey in Hungarian community pharmacies. *Acta Pol Pharm*, 5. (in press, accepted 2016.10.29.)
4. **Somogyi O**, Meskó A, Csorba L, Szabó P, Zelkó R. (2017) Pharmaceutical counselling about different types of tablet-splitting methods based on the results of weighing tests and mechanical development of splitting devices. *Eur J Pharm Sci*, 106: 262-273.

### Other publications connected to the theme of Ph.D. thesis

**Somogyi O**, Maráczsi FH, Hankó B. (2017) Egyéni egészségtervezés eredményei és lehetőségei a magyarországi gyógyszertárakban. *Gyógyszerészet*, 61: 217-223.

**Somogyi O**. (2017) A gyógyszeres tapszokkal kapcsolatos írásos tanácsadás hatékonysága. *Gyógyszertár: A Magángyógyszerészek Országos Szövetségének kiadványa*, 16: (1) 7-9.

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